MULTI-CENTRE RESEARCH ETHICS COMMITTEES

APPLICATION FORM

For official MREC Use Only	*For official MREC Use Only*
MREC/ / /	

INSTRUCTIONS: Please complete in type. Please place a circle around Yes/No options as appropriate. A version of this form is available on disc from the administrator of the MREC.

It is essential that this form is completed fully and sent with relevant enclosures. **You should not simply refer to the protocol but complete the form with the information requested.** Please refer to the accompanying Guidance Notes when completing the form and complete the checklist before sending. Where a question is not applicable it is important to make this clear and not to leave it blank. **It is important that the language used in this application is clear and understandable to lay members**. All abbreviations should be explained.

Applicant's Checklist

Please indicate if the following have been enclosed by underlining or placing a circle round Yes/No/Not applicable options.

Application Form (one copy only)	Yes	No	
Full protocol with reference details (**six** copies)	Yes	No	Not applicable
Application Fee of £1000	Yes	No	Not applicable
Research subject consent form with version number and date	Yes	No	Not applicable
Research subject information sheet with version number and date	Yes	No	Not applicable
Advertisement for research subjects	Yes	No	Not applicable
GP/consultant information sheet or letter	Yes	No	Not applicable
Interview schedules for research subjects	Yes	No	Not applicable
Letters of invitation to research subjects	Yes	No	Not applicable
Questionnaire* Finalised/Not yet finalised	Yes	No	Not applicable
Researchers brochure or data sheet for all drugs (**six** copies)	Yes	No	Not applicable
Statement regarding compensation arrangements (one copy only)	Yes	No	Not applicable
Principal Researcher c.v. (one copy only)	Yes	No	Not applicable
CTX/CTC/DDX (one copy only)	Yes	No	Not applicable
Annexe A**	Yes	No	Not applicable
Annexe B***	Yes	No	Not applicable
Annexe C****	Yes	No	Not applicable

* *Please indicate whether or not this is the final version*

** *Required if the study involves the use of a new medicinal product or medical device, or the use of an existing product outside the terms of its product licence. Annexe A is attached to the Application Form.*

*** *Required if the study includes the use of ionising, radioactive substances or X-Rays. Annexe B is attached to the Application Form.*

**** *Information concerning local researchers should always be given where possible at this stage. Annexe C is attached to the Application Form. Please make additional copies as necessary.*

SECTION 1 Details of applicant(s)

1. Short title of project (including any version dates):

Establishment of a UK Registry for adults with familial idiopathic thrombocytopenic purpura

Full title:

Establishment of a UK Registry for adults with familial idiopathic thrombocytopenic purpura (ITP) and investigation of potential causative genes

2. Principal researcher (who will be responsible for dealing with the MREC)

Surname:

Provan

Forename:

Drew

Title:

Dr

Present appointment of applicant:

Senior Lecturer in Haematology

Qualifications:

BSc MBChB DM FRCP FRCPath

Address:

Department of Haematology, St Bartholomew's & The London School of Medicine & Dentistry, London E1 1BB

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020-7377-7178

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3. Senior researcher at LEAD centre (if different from above)

Surname:

Forename:

Title:

Present appointment:

Qualifications:

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4. Who is sponsoring the study?

Contact name:

Mrs Shirley Watson, Administrator

Organisation:

The ITP Support Association (patient-based charitable organisation) is funding part of the laboratory project only.

Address:

'Synehurst', Kimbolton Road, Bolnhurst, Beds MK44 2EW

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shirley@itpsupport.org.uk

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5. Drug Company Reference Number

N/A

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6. Will researchers be paid for taking part in the study? *Yes* *No*

If so, will BMA guidelines (*Manual* II.47 - see Guidelines) **be followed?** *Yes* *No*

If not, why not?

N/A

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7. Proposed start date and duration of the study

Early 2003. This longitudinal study will run for several years.

8. What other researchers are/do you intend to be involved in this project? (Details of researchers added subsequently must be notified to the MREC)
Please use the form attached at Annexe C

The UK Adult Familial ITP Registry will be open to all haematologists and patients throughout the UK. We would hope that LREC submissions will be lodged by most UK Trusts once MREC approval obtained.

In addition, the following clinicians have expressed interest in the study and wish to take part and are willing to consent patients for cytokine gene polymorphism analysis. This will require them to fill in a simple proforma (copy enclosed) and sending 2 x 5ml EDTA samples:

Dr Alastair Smith, Department of Haematology, Royal South Hants Hospital, Southampton
Dr Virginia Clough, Department of Haematology, Countess of Chester NHS Trust, Cheshire
Dr Trevor Baglin, Department of Haematology, Addenbrooke's NHS Trust, Cambridge
Dr Vijoy Chowdhury, Department of Haematology, Broomfield Hospital, Chelmsford, Essex
Dr Eric Watts, Department of Haematology, Basildon Hospital, Basildon, Essex
Dr Isobel Walker, Department of Haematology, Royal Infirmary, Castle Street, Glasgow
Dr Mike Mills, Department of Haematology, Southend General Hospital, Westcliffe-on-Sea
Dr Miles Evans, Department of Haematology, Homerton Hospital, London
Dr Ray Majer, Department of Haematology, Prince Philip Hospital, Llanelli, Dyfed
Dr Peter Cumber, Department of Haematology, West Wales General Hospital, Carmarthen
Dr Charles Singer, Department of Haematology, Royal United Hospital, Combe Park, Bath
Dr Archie Prentice, Department of Haematology, Derriford Hospital, Plymouth, Devon
Dr Judith Marsh, St George's Hospital, Tooting, London
Dr Michael Murphy, Department of Haematology, John Radcliffe Hospital, Oxford
Dr Deane, Norfolk & Norwich Hospital, Norwich

SECTION 2 Details of project

*This section must be completed fully. A copy of the protocol should be enclosed with the application form, but it is **not** sufficient to complete questions by referring to the protocol.*

9. Aims and objectives of project *(Approx. 250 words)*

Description of ITP

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder (i.e. a disease in which an individual makes an antibody that attacks his or her own tissues) in which the production of autoantibodies to the patient's own platelet proteins results in premature platelet destruction in the peripheral circulation, mainly the spleen. This leads to a marked reduction in the peripheral blood platelet count (thrombocytopenia). ITP affects all ages and both sexes with an overall female preponderance. Since the primary role of blood platelets is to arrest bleeding, the clinical consequences of a low platelet count include bruising, mucosal bleeding, retinal haemorrhage, nosebleeds, gastrointestinal haemorrhage and excessive menstrual bleeding.

Most cases of ITP are sporadic and not inherited. The underlying abnormality (ies) leading to autoantibody production resulting in ITP are not known but from studies of other autoimmune diseases, such as rheumatoid arthritis, Crohn's disease and many others, it appears that point mutations or even natural variations (polymorphisms) within immune response genes may predispose to autoimmune disease. The same is probably true for ITP and these are discussed later. We have recently established a registry of Adult ITP (**London MREC 02/2/58**) in order to study such genes in sporadic non-familial patients.

Aims

Our aim is to study familial ITP in order to look for causative genes in this form of ITP. This may help our understanding of the mechanism of thrombocytopenia in such patients, and may help subclassify the familial thrombocytopenias into different types (it is highly likely that the term "familial thrombocytopenia" embraces several different disorders although we cannot tell them apart using current methods. We would then be able to look for similar genetic variations in the commoner sporadic form of ITP since the same genes may cause this form of the disease.

Purpose of the disease registry

Population-based disease registries are very helpful in disorders which are uncommon since single centre experience is unlikely to yield sufficient data to guide treatment, because individual hospitals will simply not have sufficient patients attending their clinics. By using a Familial ITP Registry we will be able to collate sufficient demographic and clinical information to allow us to determine the true incidence and likely outcomes; we will also learn more about the cause and biology of autoimmune diseases such as this. Through our involvement with *The ITP Support Association* we will be able to keep patients fully informed in terms of the outcome(s) of the study. In addition, registries can provide a useful medium for alerting patients to new therapies, drug trials, and other innovations.

Summary of Aims of study

- To collect retrospective and prospective data on UK adults with familial thrombocytopenia
- Determine the true incidence and prevalence of familial thrombocytopenia
- Conduct natural history study by following patients up over time (years) in order to monitor clinical outcomes
- To determine the frequency of genetic polymorphisms within a variety of immune response and other candidate genes

10. Scientific background of study *(Approx. 250 words)*

Pathogenesis of ITP

As with most autoimmune diseases the precise cause of ITP is not known. In children acute ITP typically follows a trivial viral infection, and tends to be transient, requires no treatment and recovers spontaneously (George, *et al.*, 1996). Some form of mimicry between viral and platelet proteins may be responsible for these cases. However, in most adults the disease is chronic and few patients have spontaneous recovery. ITP is usually *sporadic* although familial thrombocytopenias are well recognised but poorly understood. In some cases of familial thrombocytopenia the appearances of the platelets in the peripheral blood and bone marrow are identical to those seen in sporadic ITP and the familial nature of the disorder is only detected on direct questioning of the patient. Other forms of familial thrombocytopenia have characteristic structural platelet abnormalities not found in the sporadic form e.g. the presence of very large platelets (Becker, *et al.*, 1998). Most cases of familial thrombocytopenia are inherited in a Mendelian autosomal dominant manner where only one copy of the abnormal gene needs to be present to cause the disease (Buijs, *et al.*, 2001; Cordiano, *et al.*, 1996; Kobor, *et al.*, 1991; Kurstjens, *et al.*, 1968; Najean and Lecompte, 1990).

Despite sharing a similar mode of inheritance such familial thrombocytopenias are likely to represent several distinct disorders which appear clinically similar. For example, in one familial thrombocytopenia, in which there is a single base change in the *CBFA2* gene, there is a tendency towards the development of acute myeloid leukaemia (Buijs, *et al.*, 2001). The reason why this familial platelet disorder leads to acute leukaemia is not known.

Cytokine gene polymorphisms: their role in autoimmune disease

Cytokines are natural proteins produced by a variety of cells that co-ordinate the immune system, and control the activities of target cells involved in the normal immune response. In broad terms there are two types of response: (1) a *pro-inflammatory* Th1 response, involving CD4+ lymphocytes and (2) an *anti-inflammatory* response involving Th2 (CD8+) cells, interleukin-6 (IL-6), and other cytokines. Autoimmune diseases are believed to be influenced by the imbalance between pro- and anti-inflammatory cytokines (Cunha-Neto, *et al.*, 1998; Groux, *et al.*, 1995). Attention is now being focused on factors influencing the expression of cytokine genes; such studies have included addressing whether genetic polymorphisms within the cytokine genes influence the level of expression of individual cytokines and hence the overall immune response.

Evidence supporting the role of cytokine gene polymorphisms in autoimmune disease

Genetic linkage analysis has identified regions of chromosomal DNA that are implicated in the development of autoimmune disease. Many of these span genes for cytokines, their receptors or other immunoregulatory molecules (Becker *et al.*, 1998). A number of studies have shown a definite association between the presence of cytokine polymorphisms and development of autoimmune diseases. These include: multiple sclerosis (Miterski, *et al.*, 1999); Graves' disease (Siegmund, *et al.*, 1998); insulin-dependent diabetes mellitus (Awata, *et al.*, 1994); systemic lupus erythematosus (Nakashima, *et al.*, 1999); rheumatoid arthritis (Eskdale, *et al.*, 1998) and many others. We are already carrying out such studies in the sporadic form of ITP and would like to apply the same assays to the familial forms of the disorder.

What are the benefits of studying the genetics of familial ITP?

Attempting to identify causative genes in sporadic disorders is difficult although some headway is being made in several disease areas. One method of identifying potential genes responsible for disease is provided by the study of familial forms of the disease. If target genes are identified in familial disorders these can be helpful in analysis of the inherited forms (e.g. helps subclassify) and the sporadic forms. Available evidence to date suggests that genes playing a role in immune regulation (e.g. cytokine genes), programmed cell death (e.g. *Fas*), transcription factor genes (e.g. *CBFB2* and *GATA1*) may have a role in susceptibility to autoimmunity. The study of these genes is therefore our primary goal.

References

Awata, T., Matsumoto, C., Urakami, T., Hagura, R., Amemiya, S. & Kanazawa, Y. (1994). Association of polymorphism in the interferon gamma gene with IDDM. *Diabetologia,* **37**, 1159-1162.

Becker, P. S., Clavell, L. A. & Beardsley, D. S. (1998). Giant platelets with abnormal surface glycoproteins: a new familial disorder associated with mitral valve insufficiency. *J Pediatr Hematol Oncol,* **20**, 69-73.

Buijs, A., Poddighe, P., van Wijk, R., van Solinge, W., Borst, E., Verdonck, L., Hagenbeek, A., Pearson, P. & Lokhorst, H. (2001). A novel CBFA2 single-nucleotide mutation in familial platelet disorder with propensity to develop myeloid malignancies. *Blood,* **98**, 2856-2858.

Cordiano, I., Salvan, F., Randi, M. L., Ruffatti, M. A., Steffan, A., Girolami, A. & Fabris, F. (1996). Antiplatelet glycoprotein autoantibodies in patients with autoimmune diseases with and without thrombocytopenia. *J Clin Immunol,* **16**, 340-347.

Cunha-Neto, E., Rizzo, L. V., Albuquerque, F., Abel, L., Guilherme, L., Bocchi, E., Bacal, F. & Carrara, D. (1998). Cytokine production profile of heart-infiltrating T cells in Chagas' disease cardiomyopathy. *Brazilian Journal of Medical and Biological Research,* **31**, 133-137.

Eskdale, J., McNicholl, J., Wordsworth, P., Jonas, B., Huizinga, T., Field, M. & Gallagher, G. (1998). Interleukin-10 microsatellite polymorphisms and IL-10 locus alleles in rheumatoid arthritis susceptibility. *Lancet,* **352**, 1282-1283.

George, J. N., Woolf, S. H., Raskob, G. E., Wasser, J. S., Aledort, L. M., Ballem, P. J., Blanchette, V. S., Bussel, J. B., Cines, D. B., Kelton, J. G., Lichtin, A. E., McMillan, R., Okerbloom, J. A., Regan, D. H. & Warrier, I. (1996). Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood,* **88**, 3-40.

Groux, H., Rouleau, M., Bacchetta, R. & Roncarolo, M. G. (1995). T-cell subsets and their cytokine profiles in transplantation and tolerance. *Annals of the New York Academy of Sciences,* **770**, 141-148.

Kobor, J., Turi, S., Erdos, A., Bodrogi, T. & Virag, I. (1991). [Macrothrombopenia, nephritis and hearing loss--a new case of Epstein syndrome]. *Orv Hetil,* **132**, 1875-1877.

Kurstjens, R., Bolt, C., Vossen, M. & Haanen, C. (1968). Familial thrombopathic thrombocytopenia. *Br J Haematol,* **15**, 305-317.

Miterski, B., Jaeckel, S., Epplen, J. T., Pohlau, D. & Hardt, C. (1999). The interferon gene cluster: a candidate region for MS predisposition? *Genes and Immunity,* **1**, 37-44.

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Siegmund, T., Usadel, K. H., Donner, H., Braun, J., Walfish, P. G. & Badenhoop, K. (1998). Interferon-gamma gene microsatellite polymorphisms in patients with Graves' disease. *Thyroid,* **8**, 1013-1017.

11. Brief outline of project *(Approx. 250 words)*

Patient selection

There are several families with thrombocytopenia currently attending the General Haematology Clinic at The Royal London Hospital. These patients would be invited to take part. Because familial ITP is uncommon we are keen to involve patients from as many Trusts throughout the UK as possible. Blood samples (2 x 5 ml EDTA) will be taken and sent to the Molecular Haematology Laboratory at The Royal London Hospital after filling in a simple proforma (see Clinician Proforma). Samples will be allocated unique numbers and details entered onto the Familial ITP database.

Methods/design

We wish to collect DNA from adult patients (>18 years) with ITP; control DNA is already available with full ethical approval for its use (age and ethnically matched); control data have already been published in the literature for most DNA polymorphisms identified to date. The number of patients/controls required will depend on the frequency of the polymorphisms in the control population but we anticipate that we will require around 100–200 families and 250 control samples for each polymorphism.

We will use standard published methods to amplify DNA regions of interest using polymerase chain reaction (PCR) amplification. The presence/absence of polymorphisms within the genes encoding IL-4R, IL-10, TGF-β, TNF-α, IL-2, FcγRII & III, IL-4, IL-1α, IFN-γ, NRAMP-1, IL-6, TCRβ and CTLA-4 will be correlated with anonymised clinical data on the ITP database.

DNA will be extracted from the 10ml blood samples (EDTA) and stored at –70°C until required for polymorphism analysis.

The presence or absence of single nucleotide polymorphisms within the following genes will be determined using standard methods; key references are provided below:

Gene	***Key method reference***
Transcription factors	
CBFA2	(Ho*, et al.*, 1996)
GATA1 mutations	(Wechsler*, et al.*, 2002)
Apoptosis genes	
Fas	(Aspinall*, et al.*, 1999)
Cytokine genes already being evaluated as part of the UK Adult ITP Registry (MREC 02/2/58)	
IL-4R	(Hackstein*, et al.*, 1999)
IL-10 (x 3)	(Turner*, et al.*, 1997)
TGF-β (x 2)	(Lympany*, et al.*, 1998)
TNF-α	(Wilson*, et al.*, 1997)
IL-2	(John*, et al.*, 1998)
IL-4	(Cantagrel*, et al.*, 1999)
IL-1α	(McDowell*, et al.*, 1995)
IFN-γ	(Siegmund*, et al.*, 1998)
FcRII & III	(Jiang*, et al.*, 2000)
NRAMP-1	(Singal*, et al.*, 2000)
IL-6	(Fishman*, et al.*, 1998; Olomolaiye*, et al.*, 1998)
CTLA-4	(Heward*, et al.*, 1999)

Legend: IL, interleukin; TNF, tumour necrosis factor; TGF, transforming growth factor; IFN, interferon; CTLA, cytotoxic T lymphocyte antigen; NRAMP, natural resistance associated macrophage protein; Fcγ, Fc receptor; (x *n*), number of polymorphisms within gene.

References

Aspinall, A. I., Pinto, A., Auer, I. A. (1999). Identification of new Fas mutations in a patient with autoimmune lymphoproliferative syndrome (ALPS) and eosinophilia. *Blood Cells Mol Dis,* **25**, 227-238.

Cantagrel, A., Navaux, F., Loubet-Lescoulie, P. (1999). Interleukin-1beta, interleukin-1 receptor antagonist, interleukin-4, and interleukin-10 gene polymorphisms: relationship to occurrence and severity of rheumatoid arthritis. *Arthritis Rheum,* **42**, 1093-1100.

Fishman, D., Faulds, G., Jeffery, R. (1998). The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. *J Clin Invest,* **102**, 1369-1376.

Hackstein, H., Kluter, H., Fricke, L (1999). The IL-4 receptor alpha-chain variant Q576R is strongly associated with decreased kidney allograft survival. *Tissue Antigens,* **54**, 471-477.

Heward, J. M., Allahabadia, A., Armitage, M. (1999). The development of Graves' disease and the CTLA-4 gene on chromosome 2q33. *Journal of Clinical Endocrinology and Metabolism,* **84**, 2398-2401.

Ho, C. Y., Otterud, B., Legare, R. D. (1996). Linkage of a familial platelet disorder with a propensity to develop myeloid malignancies to human chromosome 21q22.1-22.2. *Blood,* **87**, 5218-5224.

Jiang, Y., Hirose, S., Abe, M. (2000). Polymorphisms in IgG Fc receptor IIB regulatory regions associated with autoimmune susceptibility. *Immunogenetics,* **51**, 429-435.

John, S., Turner, D., Donn, R. (1998). Two novel biallelic polymorphisms in the IL-2 gene. *Eur J Immunogenet,* **25**, 419-420.

Lympany, P. A., Avila, J. J., Mullighan, C. (1998). Rapid genotyping of transforming growth factor beta1 gene polymorphisms in a UK Caucasoid control population using the polymerase chain reaction and sequence-specific primers. *Tissue Antigens,* **52**, 573-578.

McDowell, T. L., Symons, J. A., Ploski, R. (1995). A genetic association between juvenile rheumatoid arthritis and a novel interleukin-1 alpha polymorphism. *Arthritis Rheum,* **38**, 221-228.

Olomolaiye, O., Wood, N. A. P. & Bidwell, J. L. (1998). A novel *Nla*III polymorphism in the human IL-6 promoter. *European Journal of Immunogenetics,* **25**, 267.

Siegmund, T., Usadel, K. H., Donner, H. (1998). Interferon-gamma gene microsatellite polymorphisms in patients with Graves' disease. *Thyroid,* **8**, 1013-1017.

Singal, D. P., Li, J., Zhu, Y. (2000). NRAMP1 gene polymorphisms in patients with rheumatoid arthritis. *Tissue Antigens,* **55**, 44-47.

Turner, D. M., Williams, D. M., Sankaran, D. (1997). An investigation of polymorphism in the interleukin-10 gene promoter. *Eur J Immunogenet,* **24**, 1-8.

Wechsler, J., Greene, M., McDevitt, M. A. (2002). Acquired mutations in GATA1 in the megakaryoblastic leukemia of Down syndrome. *Nat Genet,* **32**, 148-152.

Wilson, A. G., Symons, J. A., McDowell, T. L. (1997). Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. *Proc Natl Acad Sci U S A,* **94**, 3195-3199.

Patient anonymity, consent and data protection

We will only accept clinical registrations and blood samples from patients in whom there is explicit informed consent. Many adult patients with ITP have a high level of awareness of their condition through *The ITP Support Association* website and regular newsletter. Patients must be asked if they wish their data to be registered centrally at our institution and whether they wish their DNA to be tested for the polymorphisms listed above. We have already discussed the issue of data protection with the Trust Data Protection officer (Mr John Fowler) and we have registered the details of the registry with him. We will require unique patient identifiers but these will not appear within the database; instead we will allocate unique numbers to the patients and identify them using this. We will, however, need some mechanism whereby patients can be identified later in order to correlate the presence/absence of polymorphisms with outcome, and also to carry out the natural history study.

12. Study design (e.g. RCT, cohort, case control, epidemiological analysis)

Disease registry and case control/ disease association study.

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13. Size of the study (including controls)

Will the study involve:

(a) Human Subjects *Yes* *No*

i) How many patients will be recruited?

Between 100-200 affected families

ii) How many controls will be recruited?

250 per assay; DNA is already available in our department with full ethical approval obtained

iii) What is the primary end point?

Establishment of the registry, and determination of gene polymorphism frequencies within patient and control groups.

iv) How was the size of the study determined?

From known published polymorphism frequencies, with input from our Senior Biostatistician.

v) What is the statistical power of the study?

90% with alpha value 0.05.

(b) Patient Records *Yes* *No*

i) How many records will be examined?

We will use the data from simple registration proformas rather than case notes.

ii) How many control records will be examined?

None.

iii) What is the primary end point?

The genetic polymorphisms will be analysed and correlated with disease, and clinical outcomes.

iv) How was the size of the study determined?

From previously published polymorphism data.

v) What is the statistical power of the study?

90% with alpha value 0.05.

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14. Scientific critique

Has the protocol been subject to scientific critique? If so, please give the following information:

If the critique formed part of the process of obtaining funding, please give the name and address of the funding organisation:

The ITP Support Association (see above)

If the critique took place as part of an internal process, please give brief details:

External review was required in order to obtain funding, which was granted in April 2001.

If no critique has taken place, please explain why, and offer justification for this:

If you are in possession of any referees' or other scientific critique reports relevant to your proposed research, please forward copies with your application form.

We do not have copies of the referees' comments.

SECTION 3 Recruitment of subjects

15. How will the subjects in the study be:

i) selected?

Our intention is to study only adult patients with familial autoimmune thrombocytopenia (ITP). Patients in whom thrombocytopenia is caused by other underlying diseases will not be included in the study.

ii) recruited?

Adult patients with familial ITP attending clinics at Barts and London NHS Trust and other UK Trusts will be invited to take part. We will advertise the Registry in the British Society for Haematology bulletin and ITP Support Association newsletters.

iii) what inclusion criteria will be used?

Platelets <150 x 10^9/l, no other underlying autoimmune disease, adults only, other family members affected.

iv) what exclusion criteria will be used?

Patients in whom there is doubt/evidence of a secondary cause for the thrombocytopenia will be excluded; non-familial cases will be excluded from this Registry.

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16. How will the control subjects group (if used) be: *(Type N/A if no controls)*

i) selected?

Age and ethnically matched; only required for laboratory study.

ii) recruited?

Two sources (used for different assays): Our department has a large bank of fully anonymised DNA samples obtained with consent from patients undergoing DNA fingerprinting for paternity or immigration testing (Ethics approval granted). Second group comprises Blood Donors attending North London Blood Centre (Ethics approval granted).

iii) what inclusion criteria will be used?

No clinical details known regarding controls.

iv) what exclusion criteria will be used?

None.

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17. Will there be payment to research subjects of any sort? *Yes* *No*

If yes, how much per subject and for what?

SECTION 4 Consent

18. Is *written* consent to be obtained? *Yes No*

If yes, please attach a copy of the consent form to be used.

If no written consent is to be obtained, please justify.

19. How long will the subject have to decide whether to take part in the study?

If less than 24 hours please justify.

No time limit. Patients will not be pressurised into taking part.

20. Please attach a copy of the written information sheet or letter to be given to the subject.

(See Guidelines page 3 and Appendix A.)

If no Information Sheet is to be given, please justify.

21. Have any special arrangements been made for subjects for whom English is not a first language? *Yes No N/A*

If yes, give details.

For The Royal London patients, we liaise closely with the Advocates (interpreters) department; advocates routinely attend our clinics to explain diagnoses, treatments and we will seek their help in explaining the study details to patients whose first language is not English. For most other centres language should pose less of a problem and we would expect the centres to employ interpreters as required.

If no, please justify.

22. Will any of the subjects or controls be from one of the following vulnerable groups?

Children under 18 (16 in Scotland)

People with learning difficulties

Unconscious or severely ill

Other vulnerable groups e.g. mental illness, dementia

Yes No

If yes, please specify and justify:

23. What special arrangements have been made to deal with the issues of consent for the subjects above? *(Please see Guidelines.)*

N/A

SECTION 5 Details of interventions

24. Does the study involve the use of a new medicinal product or medical device, or the use of an existing product outside the terms of its product licence? *(Please see Guidelines.)* *Yes* *No*

If yes, please complete Annexe A of the Application Form.

25. Will any ionising or radioactive substances or X-Rays be administered? *Yes* *No*

(NB Please ensure information in Question 14 includes exclusion criteria with regard to ionising radiation if appropriate.)

If yes, please complete Annexe B of the Application Form.

26. Please list those procedures in the study to which subjects will be exposed indicating those which will be part of normal care and those that will be additional (e.g. taking more samples than would otherwise be necessary). Please also indicate where treatment is withheld as a result of taking part in the project.

10 ml EDTA blood will be obtained, at the same time as the standard 5 ml EDTA for the patients' routine clinic blood count. One venepuncture only will be required, so patients will experience no additional discomfort. The volume of blood drawn is very small (15 ml in total) and therefore non-hazardous.

SECTION 6 Risks and ethical problems

27. Are there any potential hazards? *Yes* *No*

If yes, please give details, and give the likelihood and details of precautions taken to meet them, and arrangements to deal with adverse events.

28. Is this study likely to cause any discomfort or distress? *Yes* *No*

If yes, please give details and justify.

29. What particular ethical problems or considerations do you consider to be important or difficult with the proposed study?

Please give details.

None.

30. Will information be given to the patient's General Practitioner? *Yes* *No*

Please note: permission should always be sought from research subjects before doing this.

If yes, please enclose an information sheet/letter for the GP.

If no, please justify:

We are collecting population data in order to determine the frequency of particular genetic polymorphisms in an autoimmune disease. It is unlikely that a single patient's results will be meaningful in itself.

31. If the study is on hospital patients, will consent of all consultants whose patients are involved in this research be sought? *Yes* *No*

If no, please justify:

Outpatients only.

SECTION 7 Compensation and confidentiality

Product liability and consumer protection legislation make the supplier and producer (manufacturer) or any person changing the nature of a substance, e.g. by dilution, strictly liable for any harm resulting from a consumer's (subject or patient) use of a licensed product.

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32. Have arrangements been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, a subject for non negligent harm?
(Please indicate N/A if not applicable)

Yes No N/A

N/A

If yes, please give details of compensation arrangements with this application.

For NHS-sponsored research, HSG(96)48 reference no. 2 refers.

For pharmaceutical company sponsored research, the company should confirm that it will abide by the most recent ABPI guidelines *(Manual V.14.1.1)*

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33. In cases of equipment or medical devices, have appropriate arrangements been made with the manufacturer to provide indemnity?

(Please indicate N/A if not applicable) *Yes No N/A*

If yes, please give details and enclose a copy of the relevant correspondence with this application.

N/A

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34. Will the study include the use of any of the following?

Audio/video recording *Yes No*

Observation of patients *Yes No*

If yes to either:

i) How are confidentiality and anonymity to be ensured?

ii) What arrangements have been made to obtain consent for these procedures?

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35. Will medical records be examined by research worker(s) outside the employment of the NHS? *Yes No*

If yes, please see Guidelines.

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36. What steps will be taken to safeguard confidentiality of personal records?

Records will only be examined by the physicians who are caring for the patients.

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37. What steps will be taken to safeguard the information relating to specimens and the specimens themselves?

Samples will be given unique trial numbers in order to anonymise. Data will be held on one computer and the database will be password protected.

PLEASE ENSURE THAT YOU COMPLETE THE CHECKLIST ON THE FRONT COVER OF THE APPLICATION FORM AND ENCLOSE ALL RELEVANT ADDITIONAL DOCUMENTS.

SECTION 8 Declaration

DECLARATION

The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

I understand it is my responsibility to obtain management approval where appropriate from the relevant NHS body before the project takes place.

I agree to supply interim and final reports on the pro forma provided, and to advise my sponsor, the MREC from which approval was granted for this proposal and any local researchers taking part in the project of any adverse or unexpected events that may occur during this project.

Signature of Principal Researcher: .....…….....

Date:.....

Annexe A — Drugs and Devices

This form is to be used if the study involves the use of a new medical product or medical device, or the use of an existing product outside the terms of its produce licence.

i) **Is a pharmaceutical or other commercial company arranging this trial?** *Yes* *No*

If no, has approval of the licensing authority been obtained by means of a DDX? *Yes* *No*

ii) **Does the drug(s) or device have a product licence(s) for the purpose for which it is to be used?** *Yes* *No*

If yes, please attach data sheet or equivalent.

iii) **Is any drug or medical device being supplied by a company with a Clinical Trial Certificate or Clinical Trial Exemption?** *Yes* *No*

Please attach CTC, CTX, or DDX.

iv) **Has a CTC, CTX or DDX been applied for but not yet received?** *Yes* *No*

If so, the application can be made but a valid CTX must be provided to the MREC before the research can proceed

v) **Details of drugs to be used** *(Please complete the table below for each drug making additional copies of this page as necessary)*

Approved Name(s):

Generic Name:

Trade Name:

Strength	Dosage and Frequency	Route	Duration of Course

vi) **When Drugs not listed in the British National Formulary are being used, applicants should provide the following information on not more than 3 sides of A4 paper :**

a) **What is the formulation, purity and source of the Drug ?**

b) **What are the pharmacological actions of the Drug - including those not relevant to the proposed therapeutic indications ?**

c) **Toxicology - including details of species, number of animals, doses, duration of treatment and route(s) of administration. Important findings should be summarised.**

d) **Clinical pharmacology in Man including :**

- Extent of Use in Man
- Dosage schedules used - dose, route, duration
- Side effects and their frequency
- Information on duration of action and mechanism of elimination, if known.

e) **Applicant's experience with this drug in man. Give brief information on previous studies, number and type of subjects and nature and incidence of side effects.**

vi) **Details of Medical Device**

vii) **If an electrical device, has the device been through acceptance and safety testing?** *Yes* *No*

Give details:

Annexe B Radiation

This form is to be used if the study involves the use of additional ionising or radioactive substances or X-Rays.

a) RADIOACTIVE SUBSTANCES

i) Details of substances to be administered *(Please complete the table below)*

Investigation:

Radionucleide

Chemical form

Quantity of radio-activity to be administered (MBq)	Route	Frequency

ii) Estimated Effective Dose (Effective Dose Equivalent) (mSv):
(Please supply source of reference or attach calculation)

iii) Absorbed dose to organ or tissues concentrating radioactivity (mGy) (Specify dose and organ)
(Please supply source of reference or attach calculation)

b) X-RAYS

i) Details of radiographic procedures

Investigation	Organ(s)	Frequency

ii) Estimated Effective Dose (Effective Dose Equivalent) (mSv):
(Please supply source of reference or attach calculation)

Annexe C	Local Researchers

OTHER RESEARCHERS INVOLVED IN THIS STUDY

Please provide the name and contact details of other researchers involved in this study. Please include your own name and centre if you are also a local researcher.

(Please copy and complete this page for each researcher. You must inform the MREC Administrator by means of a copy of this form as each new researcher is recruited.)

MREC Reference Number:

This Registry will potentially involve all UK Trusts and hence not all are listed here. Those expressing a desire to take part in the study, to date, are shown in Section 8.

Name

Contact Address:

Location of research
(if different):

Telephone:

Fax:

E-Mail:

Please retain a blank copy of this form, complete it and send to the MREC Administrator whenever other local researchers become involved in the future.

Annexe D Supplementary Form for LRECs

SUPPLEMENTARY FORM FOR LOCAL ARRANGEMENTS

To be completed by the local researcher or principal researcher if appropriate (please see guidelines) once MREC approval has been obtained.

Please send this signed and completed form to the appropriate LREC administrator together with the **appropriate number** of copies of::

the MREC application form
the MREC letter of approval
the signed MREC response form.
the local researcher's c.v.
the consent form and information sheet

together with **one** copy of the protocol

If you require help with the address of your appropriate LREC please seek advice from the MREC Administrator.

1 MREC Reference Number:

2. Short title of project

3. Details of lead of local investigator:

Surname:

Forename:

Title:

Present Appointment:

Qualifications:

4. Please give an approximate figure for the number of trials/studies in which the principal researcher has been involved over the past year

5. Proposed start date and duration of project

6. Names, titles and qualifications of other local researchers working on this project

7. Location of project

8. Funding

Please give full details where applicable of:

a) Payment to subjects

b) Payment to Trust/practice/research funds

c) Personal payment or personal benefit to researcher

Is payment:

i) A block grant ***Yes*** *No*

ii) Based on the number of research subjects recruited? *Yes* *No*

If yes, how much per patient:

d) Details of other benefits, e.g. equipment

e) Will the costs incurred by the institution be covered by the payment? *Yes* *No*

9. Local Recruitment of Subjects

a) How many subjects are being studied locally?

b) Are any of these subjects involved in existing research or have been involved in any recent research in the last six months? *Yes* *No*

If yes, please justify their use in this project

c) **Will any of the subjects involved be in a dependent relationship with the researcher?** *Yes* *No*

If yes, please ensure you comply with local recruitment arrangements

d) **Will any of the subjects involved be medical students?** *Yes* *No*

If yes, please obtain signed agreement of the Principal of the Medical School:

Signature of Principal of Medical School: .....

10. Local Safety Requirements

a) **Are you going to administer radioisotopes?** *Yes* *No*

i) **If yes, do you have an ARSAC certificate?** *Yes* *No*

ii) **Have you informed the local radiation officer?** *Yes* *No*

Signature of Radiation Safety Officer: .....

b) **If you are going to administer drugs what arrangements have you made to store, code and administer them?**

Signature of Hospital Pharmaceutical Officer: .....

c) **Local emergency contact details:**

d) **Local independent adviser details:**

DECLARATION

I have read and understood the MREC form and the supplementary form for LRECs, the protocol, guidelines and all documents pertaining to this research approved by the MREC that I now enclose. The information therein and above is accurate to the best of my knowledge and belief and I take full responsibility for it.

I understand it is my responsibility to obtain management approval where appropriate from the relevant NHS body before the project takes place.

I confirm that this research will comply with all relevant UK legislation, including the Data Protection Act and the Access to Medical Records Act.

I agree to supply interim and final reports to my LREC as required.

I agree to advise my sponsor, the LREC and MREC from which approval was granted for this proposal of any adverse or unexpected events that may occur during this project. I also agree to advise the LREC if this is withdrawn or not completed.

Signature of Local Investigator: …….....……..

Date: …….....…….